General

Guideline Title

The role of initial chemotherapy for the treatment of adults with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline.

Bibliographic Source(s)

Ziu M, Kalkanis SN, Gilbert M, Ryken TC, Olson JJ. The role of initial chemotherapy for the treatment of adults with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):585-607. [21 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Target Population

Adult patients (older than 18 years of age) with newly diagnosed World Health Organization (WHO) grade II gliomas (oligodendroglioma, astrocytoma, mixed oligo-astrocytoma).

Question

Is there a role for chemotherapy as adjuvant therapy of choice in treatment of patients with newly diagnosed low grade gliomas?

Recommendation

Level III. Chemotherapy is recommended as a treatment option to postpone the use of radiotherapy, to slow tumor growth and to improve progression free survival (PFS), overall survival (OS) and clinical symptoms in adult patients with newly diagnosed low grade glioma.

Question

Who are the patients with newly diagnosed low grade glioma that would benefit the most from chemotherapy?

Recommendation

Level III. Chemotherapy is recommended as an optional component alone or in combination with radiation as the initial adjuvant therapy for all patients who cannot undergo gross total resection (GTR) of a newly diagnosed low grade glioma. Patient with residual tumor >1 cm on post-operative magnetic resonance imaging (MRI), presenting diameter of >4 cm or older than 40 years of age should be considered for adjuvant therapy as well.

Question

Are there tumor markers that can predict which patients can benefit the most from initial treatment with chemotherapy?

Recommendation

Level III. The addition of chemotherapy to standard radiation therapy is recommended in low grade glioma patients that carry IDH mutation. In addition, temozolomide (TMZ) is recommended as a treatment option to slow tumor growth in patients who harbor the 1p/19q co-deletion.

Question

How soon should the chemotherapy be started once the diagnosis of low grade glioma is confirmed?

Recommendation

There is insufficient evidence to make a definitive recommendation on the timing of starting chemotherapy after surgical/pathological diagnosis of low grade glioma has been made. However, using the 12 weeks mark as the latest timeframe to start adjuvant chemotherapy is suggested. It is recommended that patients be enrolled in properly designed clinical trials to assess the timing of chemotherapy initiation once diagnosis is confirmed for this target population.

Question

What chemotherapeutic agents should be used for treatment of newly diagnosed low grade glioma?

Recommendation

There is insufficient evidence to make a recommendation of one particular regimen. Enrollment of subjects in properly designed trials comparing the efficacy of these or other agents is recommended so as to determine which of these regimens is superior.

Question

What is the optimal duration and dosing of chemotherapy as initial treatment for low grade glioma?

Recommendation
Insufficient evidence exists regarding the duration of any specific cytotoxic drug regimen for treatment of newly diagnosed low grade glioma. Enrollment of subjects in properly designed clinical investigations assessing the optimal duration of this therapy is recommended.

Question

Should chemotherapy be given alone or in conjunction with radiation therapy as initial therapy for low grade glioma?

Recommendation

Insufficient evidence exists to make recommendations in this regard. Hence, enrollment of patients in properly designed clinical trials assessing the difference between chemotherapy alone, radiation therapy

alone or a combination of them is recommended.

Question

Should chemotherapy be given in addition to other type of adjuvant therapy to patients with newly diagnosed low grade glioma?

Recommendation

Level II. It is recommended that chemotherapy be added to the radiation therapy in patients with unfavorable low grade glioma to improve their progression free survival.

Definitions

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of Recommendation on Diagnosis

Class I evidence/Level I (or A) recommendation	Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class II evidence/Level II (or B) recommendation	Evidence provided by one or more well-designed clinical studies of a *restricted* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class III evidence/Level III (or C) recommendation	Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diffuse low grade glioma (World Health Organization [WHO] grade II gliomas [oligodendroglioma, astrocytoma, mixed oligo-astrocytoma])

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Neurology

Oncology

Intended Users

Physicians

Guideline Objective(s)

To formulate guidance for treatment of newly diagnosed low grade gliomas and to identify areas that require additional studies

Target Population

Adult patients (older than 18 years of age) with newly diagnosed World Health Organization (WHO) grade II gliomas (oligodendroglioma, astrocytoma, mixed oligo-astrocytoma)

Interventions and Practices Considered

1. Chemotherapy as adjuvant therapy
2. Chemotherapy alone or in combination with radiation therapy
3. Use of tumors markers (1p/19q co-deletion) to predict which patients can benefit from initial chemotherapy
4. Use of temozolomide (TMZ) in patients who harbor the 1p/19q co-deletion

Note: The following were recommended, but there was insufficient evidence to make a recommendation: timing of chemotherapy, optimal chemotherapy regimens, optimal duration of chemotherapy.

Major Outcomes Considered

- Tumor growth rate
- Survival rate (progression free, overall)
- Radiologic response rate
- Seizure control/improvement of seizures
- Toxicity of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Examination Approach

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of low grade gliomas. The MEDLINE and EMBASE electronic databases were searched from 1990 through 2012, with additional data being gleaned from the Cochrane Database of Systematic

Reviews, Cochrane Controlled Trials Registry, and Cochrane Database of Abstracts of Reviews of Effects. The search strategies used a combination of subheadings and text words with the specifics of this work being outlined in each guideline section. Reference lists of the publications chosen for full text review were also screened for potentially relevant studies.

Study Selection

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the writing group. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more in depth information available. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Specific Search Strategy for This Guideline

Literature Review

The following databases were searched from January 1990 to December 2012 using low-grade glioma and surgery relevant search MeSH and non-MeSH search terms: PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) was searched using Endnote (Thomson Reuters, Inc. http://www.endnote.com). The keywords used during the search in the medical literature search engines cited above are documented in Table 2 in the original guideline document. Manual searches of the included articles' bibliographies were also conducted.

Article Inclusion and Exclusion Criteria

For literature to be included for consideration, studies published in full as peer review papers had to meet the following criteria:

- Be published in English
- Involve patients with newly diagnosed World Health Organization (WHO) grade II astrocytoma, oligo-astrocytoma, or oligodendroglioma
- Involve adult patients (age over 18) or provide isolated results for adult patients in a mixed cohort
- Fully published, peer-reviewed articles
- The number of study participants with newly diagnosed low grade glioma was at least 5 for each study arm
- Use of chemotherapy after diagnosis of low grade glioma has been made
- Supratentorial low grade glioma only

Study Selection

After an extensive search, more than 1739 articles were found. The duplicates from the search in different databases were eliminated. By reviewing the titles and/or abstracts, the authors excluded all articles referring to anaplastic gliomas or glioblastomas, those discussing exclusively chemotherapy in patients younger than 18 years of age, and glioma of the spine, optic nerve, brain stem and/or posterior fossa. The authors excluded as well those publications that discussed exclusively chemotherapy used for treatment of recurrent/progressive low grade glioma and all articles discussing experimental therapy in animal tumor models. The remaining 101 articles underwent full text review. Only 13 articles met all of the inclusion criteria and were used in formulating these evidence-based clinical guidelines (see Table 2 in the original guideline document). The majority of the remaining 88 articles that underwent full review were excluded because they reported the use of chemotherapy at recurrence or progression together with its use for the initial treatment and with results that were not separable, and the remainder because they

lacked significance for the topic.

Number of Source Documents

Only 13 articles met all of the inclusion criteria and were used in formulating these evidence-based clinical guidelines (see Table 2 in the original guideline document).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence and Levels of Recommendation on Diagnosis

Class I evidence/Level I (or A) recommendation	Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
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Class III evidence/Level III (or C) recommendation	Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Evidence Analysis

Quality Assessment and Statistical Methods

Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Studies which met the eligibility criteria were subject to more detailed scrutiny and had their data extracted by one reviewer and the extracted information was checked by one or more other reviewers. Evidence and summary tables, reporting the extracted study information and evidence classification, were generated for all of the included studies for each of the questions. Evidence tables were created with most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class and conclusion. The authors were directed to craft the data in the tables in a succinct and fact filled manner so as to allow for understanding of the literature entry. The literature in the evidence tables was

expanded upon in the scientific foundation of each section so as to emphasize important points supporting its classification and contribution to recommendations. The method by which this was accomplished is expanded upon in the Joint Guideline Committee Guideline Development Methodology document (see the "Availability of Companion Documents" field). Internal drafts of the tables and manuscripts were developed by sharing between writers electronically, by telephone and meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent.

Specific Evidence Analysis for This Guideline

Evidence Classification and Recommendation Levels

Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee on criteria (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Panel Development

Recognizing the serious nature of low grade gliomas along with the lack of consensus among various treatment options, the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management and treatment of low grade glioma patients. The objectives of these guidelines are to establish the best evidence-based management of low grade gliomas in terms of imaging diagnosis, use of surgical biopsy and resection, assessment of tumor pathology, administration of systemic chemotherapy, and administration of radiation therapy. Because these tumors dependably recur or progress despite standard therapy, the Joint Tumor Section also recommended an evidence-based guideline be developed for progressive low grade gliomas and that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead writers of each section. These writers, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. Writers were provided training on the method of guideline development as used in this guideline set by written methods and instructions. The senior authors and CNS Guidelines Manager then worked with them on a step by step basis to confirm that the methods were followed as the literature was collected, assessed and documents developed. When writers were approached and preliminarily agreed to participate they were asked to complete a formal conflict of interest questionnaire confirming the appropriateness of their participation. At that point they also agreed to report any new conflicts of interest that might develop during the writing process. In this manner a multidisciplinary panel of writers referred to as the Low Grade Glioma Guidelines Task Force was assembled, with significant administrative, logistical and analytical support from the national CNS Guidelines Committee. The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

Topic Range of This Systematic Review and Clinical Practice Guideline

Having identified writing groups for each topic, the members designed questions to allow assessment of

the literature in a manner that would provide guidance for management of low grade gliomas. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of imaging assessment, diagnostic biopsy, surgical resection, tumor evaluation by standard neuropathology and molecular techniques, radiation therapy, chemotherapy, emerging therapies and treatment of recurrent or progressive low grade gliomas.

Guideline Panel Consensus

Multidisciplinary writing groups were created for each section based on author expertise, in order to address each of the disciplines and particular areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and scientific foundations for their specific section and discipline. Using this information, the writing groups then drafted the recommendations in answer to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire clinical guideline panel to allow for multidisciplinary feedback, discussion, and ultimately approval.

Rating Scheme for the Strength of the Recommendations

See the "Rating Scheme for the Strength of the Evidence" field.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Approval Process

The completed evidence-based clinical practice guidelines for the management of low grade gliomas were presented to the Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) for review. The reviewers for the Joint Guidelines Committee were vetted by the *Journal of Neuro-oncology* for suitability and expertise to serve as reviewers for the purposes of publication in that journal also. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in the *Journal of Neuro-oncology*.

The funding agencies (CNS Executive Committee and AANS/CNS Joint Tumor Section Executive Committee) were permitted to review these guidelines only after the Joint Guidelines Committee had completed its extensive review, critique and ultimate approval process; the funding groups then were limited to whether or not to endorse or reject this body of work but substantive changes were not allowed.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved survival, seizure frequency and control, and aphasia

Potential Harms

Toxicity of chemotherapy and chemoradiation regimens includes thrombocytopenia and leukocytopenia, pulmonary histiocytosis, neurotoxicity (lethargy and peripheral neuropathy), and secondary malignancies. Refer to the evidence tables in the original guideline document for toxicities reported in published studies.

Qualifying Statements

Qualifying Statements

The information in these guidelines reflects the current state of knowledge at the time of completion. Each section is designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Ziu M, Kalkanis SN, Gilbert M, Ryken TC, Olson JJ. The role of initial chemotherapy for the treatment of adults with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):585-607. [21 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Dec

Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

These guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) Guidelines Committee, with no funding from any outside commercial sources. Development of this set of evidence-based clinical practice guidelines was editorially independent from the funding agencies.

Guideline Committee

American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee

Low Grade Glioma Guidelines Task Force

Composition of Group That Authored the Guideline

Authors: Mateo Ziu, Department of Neurosurgery, Seton Brain and Spine Institute, Austin, TX, USA; Steven N. Kalkanis, Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA; Mark Gilbert, Center for Cancer Research, Neuro-Oncology Branch at National Cancer Institute, Bethesda, MD, USA; Timothy C. Ryken, Department of Neurosurgery, Kansas University Medical Center, Kansas City, KS, USA; Jeffrey J. Olson, Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Financial Disclosures/Conflicts of Interest

Conflict of Interest

Low Grade Glioma Guidelines Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Disclosures

Dr. Kalkanis is a consultant for Arbor and Varian. Dr. Olson is a consultant for the American Cancer Society; has received research funding from the National Cancer Institute, Genentech, and Millennium; and has received investigational drug provision from Merck.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Neuro-Oncology Web site.

Availability of Companion Documents

The following are available:

Rock J. Low grade glioma guidelines: foreword. J Neurooncol. 2015 Dec;125(3):447-8. Available from the Journal of Neuro-Oncology Web site.

Olson JJ, Kalkanis SN, Ryken TC. Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J Neurooncol. 2015 Dec;125(3):449-56. Available from the Journal of Neuro-Oncology Web site.

Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. [2 references]. Available from the Congress of Neurological Surgeons Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 7, 2016. The information was not verified by the guideline developer.

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